CHALLENGING TREATMENT IN MANAGING MAJOR DEPRESSION WITH SUICIDAL IDEATION IN ADOLESCENT PATIENT: A CASE REPORT OF OFF-LABEL ESKETAMINE NASAL SPRAY USAGE

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Abstract

Major Depressive Disorder (MDD) is the third most common mental disorder in adolescents. MDD causes diminished quality of life, functional impairment, poor socio-economic outcomes, and increases the risk for suicide. Suicidal ideation is present and appears to be a precondition for suicide attempts in patients with MDD, especially in adolescent patient. Around 1.4% of adolescent patient reported that they had suicidal ideation. This emphasizes the need for treatment options with sustained efficacy and long-term tolerability. In recent years, ketamine has received attention as an antidepressant agent, demonstrating promising results as well as having anti-suicidal properties. Esketamine nasal plus an oral antidepressants have demonstrated a statistically significant or clinically meaningful reduction in depressive and showed improvement in measures of depressive symptoms and other efficacy assessments during the induction phase (first 4 weeks of exposure), which appeared to be sustained during the optimization/maintenance phase. As reported in this case, After the first four weeks, patient showed improvement regarding mood and decreasing suicidal ideation as well as successful in decreasing the dosage his of oral medication.

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Introduction

More than a third of all adolescents (34.9%) showed some mental problem within the past 12 months of their life. There were no visible differences in patterns between men and women or between younger teenagers (10-13 years) and older teenagers (14-17 years). Anxiety is the most common mental health problem for adolescent boys (25.4%) and female teenagers (28.2%). Adolescent girls (6.7%) have a higher prevalence of depression compared to male adolescents (4.0%), while male adolescents have a higher prevalence of behavioural problems higher (3.5% vs 1.2%) and problems related to attention deficit and/or hyperactivity (12.3% vs 8.8%) than female adolescents.7

Major depressive disorder (MDD) is the third most common mental disorder in adolescents. MDD is a mood disorder characterized by persistent sadness and other symptoms of a major depressive episode without accompanying episodes of mania or hypomania or mixed episodes of depressive and manic or hypomanic symptoms, included in DSM-IV-TR, DSM-5, and DSM-5-TR.4 MDD has been ranked as the third cause of the burden of disease worldwide in 2008 by WHO, which has projected that this disease will rank first by 2030.13

Diagnosis of MDD according to DSM-5 includes Five (or more) of the following symptoms that have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure :

1. Depressed most of the day, nearly every day as indicated by subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful).

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by subjective account or observation).

3. Significant weight loss when not dieting or weight gain (e.g., change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.

4. Insomnia or hypersomnia nearly every day.

5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

6. Fatigue or loss of energy nearly every day Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

7. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

8. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning; The episode is not attributable to the physiological effects of a substance or to another medical condition; The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders; There has never been a manic episode or a hypomanic episode.3

MDD causes diminished quality of life, functional impairment, poor socio-economic outcomes, and increases the risk for suicide.5 The World Health Organization (WHO) estimates the suicide rate at 10.6 per 100,000 population (7.7 for females and 13.5 for males). Suicidal ideation is present and appears to be a precondition for suicide attempts in patients with major depressive disorder .The prevalence of suicidal ideation among MDD patients ranges from 4.4% to 86.7%.11 People with MDD were 5.3 times more likely to report suicidal ideas and 3.2 times more likely to attempt suicide when compared to people with mild depression. In both Hong Kongese (average age of 15.7 years old) and American (average age of 15.9 years old) students, MDD predisposed to suicidal ideation.18 Suicidal ideation is episodic, and has quick onset and short duration. It is difficult to monitor and intervene suicidal ideation in real time.11 Suicidal ideation usually precedes suicide attempts and consummated suicide, encompasses characteristics such as self-destructive thoughts, and wishes plans possessed by individuals who have the purpose of ending their lives.6

Based on data from the National Police's Criminal Information Center (Pusiknas), there were 971 suicide cases in Indonesia during the period of January to October 18 2023. This number has exceeded suicide cases throughout 2022, which amounted to 900 cases. Meanwhile globally, according to data from the World Health Organization (WHO), as of August 28 2023, more than 700,000 people die by suicide every year. According to a research by I-NAMHS (2022), several teens reported suicidal behaviour in the past 12 months. Among the entire sample, 1.4% reported that they had suicidal ideation, 0.5% had made plans to commit suicide themselves, and 0.2% reported that they had attempted suicide in the past 12 months. Almost 80% of adolescents that reported suicidal behaviour (thinking about, planning, and/or attempting) within 12 months have experienced a mental disorder.7

Treatments given to patients during the acute stage of a severe depressive episode is to assist them in entering a state of remission and ultimately returning to their pre-attack level of functioning. Pharmacotherapy, depression-focused psychotherapy, medication-assisted psychotherapy, and somatic therapies like electroconvulsive therapy (ECT) are among the choices for acute phase treatment.1 First-line antidepressants for the treatment of MDD with suicidal ideations are usually SSRIs (selective serotonin reuptake inhibitors) or SNRIs (serotonin and norepinephrine reuptake inhibitors). This is because they generally have fever and less severe side effects compared to other antidepressants. After the administration of antidepressant without improvement shown, the condition can be categorized as treatment-resistant depression.10

In recent years, ketamine has received attention as an antidepressant agent,

demonstrating promising results as well as having anti-suicidal properties.22 Nasal spray esketamine, the S-enantiomer of the anesthetic agent and dissociative drug ketamine, was approved by the FDA to treat MDD with suicide ideation in 2019. Ketamine is an N-methyl-D-aspartate receptor antagonist with the enantiomers arketamine and esketamine. Nasal esketamine has an estimated mean bioavailability of 48%,11 with hepatic first-pass avoided through this route.10 Clinical research suggests that esketamine, combined with an oral antidepressant, has a sustainable antidepressant effect as well as a manageable safety profile. However, ketamine has abuse potential and may cause adverse effects that require medical attention.14 Although esketamine has been found to be useful in treating MDD with suicidal ideations in adults and has been licensed for this purpose in a number of countries, there has been less research done on the use of this psychopharmacological agent in adolescences.22

Case report

A 15-years-old male (weight 80kg) brought by his father to mental facility with suicide attempt. Patient try to jump from the second floor of his house but were caught by his father. Patient was taken by his father to mental facility after the failed attempt. Patient had history of multiple suicidal ideations and attempts since two years ago. Patient was homeschooled after getting dropped out by his school three times. Patient were treated with escitalopram 20 mg once daily, clobazam 10 mg twice daily for the past months. Patients travelled to Jakarta and Malaysia for treatment before with no significant improvement shown.

After admitted to the mental facility, the initial assessment of the patient showed depressed mood, narrow affect, visual hallucination, and decreased psychomotor with Montgomery and Asberg Depression Rating Scale (MADRS) measured 24. Patient was given aripiprazole 10 mg once daily at morning and clozapine 50 mg once daily at night in addition to escitalopram 20 mg. Patient was placed inside observation room for the duration of treatment because of multiple suicidal ideations and attempts. Six week after medicated, patient still displayed unstable emotion and have suicidal ideation. Patient's family then were given information about esketamine nasal spray for treatment-resistant depression. Patient had a medical check up with echocardiography and MRI that came out normal.

Patient started esketamine nasal spray with a dose of 56 mg twice a week for the first four week during induction period. After the first four weeks, patient showed improvement regarding mood and decreasing suicidal ideation with a MADRS measured 12. For maintenance period, treatment continued by 56 mg once a week from week five to week eight then 56 mg once every two week from week nine to week twelve. After completing the course of treatment, patient's were successful in decreasing the dosage of oral medication to escitalopram 10 mg once a day and brexpiprazole 1mg once a day for maintenance. Patient was able to control his suicidal idea and finally admitted back to school.

Discussion

Patients with MDD and suicidal ideation have higher rates of relapse, suicidal rates and marked declines in daily functioning and health-related quality of life in comparison to patients with major depressive disorder who does not have suicidal ideation. This emphasizes the need for treatment options with sustained efficacy and long-term tolerability.23

Guidelines for the treatment of suicidality are limited with evidence mostly for reduction in suicidal ideation (SI) as opposed to suicide attempts and completions. Current options with reliable evidence of anti-suicidal effects include: lithium, clozapine, ketamine, and certain psychotherapies.21 However, the time to effect of this treatment in comparison to intranasal esketamine is one of its drawbacks. Transcranial magnetic stimulation (TMS) and electroconvulsive treatment (ECT) are non-pharmacological solutions for MDD with suicidal ideation, but they require specialized personnel and facilities. This involves having access to the right anesthetic expertise in the case of ECT.19

The FDA-approved esketamine intranasal spray (single-use) is convenient for outpatients – relative, for example, to ECT – and maximises access to therapy. Intranasal esketamine signifies an easier method of administration than IV administration of ketamine, with a rapid onset of action, reasonable bioavailability, and being more practical and less resource-demanding.15 Ketamine improves brain plasticity (via increased neuronal dendritic growth and improved synaptogenesis) by stimulating the production of brain-derived neurotrophic factor (BDNF) and by activating the mammalian target of rapamycin (mTOR). Ketamine has a more direct stimulating action on BDNF and mTOR compared to oral antidepressants.16 It acts as a non-selective, non-competitive antagonist of the NMDA receptor – an ionotropic glutamate receptor – to regulate neurotrophic signalling, and may restore synaptic function relating to the regulation of mood and emotional behaviour.

Adverse effects is foremost concern in using esketamine. The five most common adverse effects reported in the esketamine and antidepressant group during the maintenance phase were dysgeusia, vertigo, dissociation, somnolence, and dizziness.9 According to the study by Wajs et al (2020), most adverse events were not clinically significant, were mild or moderate in intensity, and were transient. Nearly all adverse events of dissociation and sedation occurred and resolved on the day of dosing.20

Esketamine nasal spray (28, 56 or 84 mg) plus an oral antidepressants have demonstrated a statistically significant or clinically meaningful reduction in depressive symptoms within the first 24 hour compared with an oral antidepressants plus placebo, and sustained decreased risk of relapse among stable remitters and responders in long-term trials.2 Research conducted by Zaki N et al (2023) showed improvement in measures of depressive symptoms and other efficacy assessments during the induction phase (first 4 weeks of exposure), which appeared to be sustained during the optimization/ maintenance phase.23

The recommended dosage of esketamine nasal spray administration in adults with MDD with acute suicidal ideation or behavior is 84 mg (3 devices; 28 mg per device) twice per week for 4 weeks. Dosage may be reduced to 56 mg twice per week based on tolerability. After 4 weeks of treatment with esketamine nasal spray, evidence of therapeutic benefit should be evaluated to determine need for continued treatment. The use of esketamine nasal spray, in conjunction with an oral antidepressant, beyond 4 weeks has not been systematically evaluated in the treatment of depressive symptoms in patients with MDD with acute suicidal ideation or behaviour.

Case report by Skala, et al (2023) reported a female adolescent patient that received esketamine 28 mg nasal spray twice a week for the first 4 weeks, then 28 mg once a week for 3 weeks. Patient showed changes in mood and suicidal ideation with MADRS decreased from 44-30 with no major adverse effects recorded.17

In this case report, a male adolescent patient was given esketamine nasal spray 56 mg for the first 4 weeks continued by 56 mg once a week from week five to week eight then 56 mg once every two week from week nine to week twelve. Patient displayed improvement regarding mood and decreasing suicidal ideation with a MADRS decreased from 24 to 12.

Esketamine nasal spray appears to provide a potentially effective treatment option for adolescents, however there are still unanswered problems regarding the safety of ketamine use in the developing adolescent brain. It has been noted that there is insufficient research on the long-term effects of recurrent ketamine use in adolescents, and that there is currently no recognized risk associated with giving ketamine to vulnerable patient populations because depressive states may also be a premorbid psychotic symptom.17

Conclusion

Many trials have demonstrated the effectiveness of intranasal esketamine in lowering depression symptoms with suicidal ideations. Given its rapid effect, it may also be considered as a bridging therapy in the future, while conventional oral antidepressants take effect. Esketamine, combined with an oral antidepressant, has a sustainable antidepressant effect as well as a manageable safety profile. Most adverse events were not clinically significant, were mild or moderate in intensity, and were transient that resolved on the day of dosing. In this case report, after the first four weeks, patient showed improvement regarding mood and decreasing suicidal ideation as well as successful in decreasing the dosage his of oral medication. However, further research is necessary to determine whether this therapeutic benefit is clinically useful in the general population, especially in adolescent and to further elucidate the potential for abuse.

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